Journal of Surgical Oncology 1998;67:60–70

REVIEW ARTICLE

Brachytherapy in Lung Cancer

LAURIE E. GASPAR, MD*
Department of Radiation Oncology, Wayne State University, Detroit, Michigan, in affiliation with the Karmanos Cancer Institute, Detroit, Michigan

Brachytherapy, the direct application of a radioactive isotope into the tumor bed, delivers a high dose to the tumor as compared to the surrounding normal tissue. Interstitial brachytherapy, the placement of the isotope into a tumor bed where no lumen exists, has been described but is utilized infrequently in clinical practice. Endobronchial brachytherapy, the placement of the source within the airway lumen, as a boost to conventional external beam radiation has not yet demonstrated improved local tumor control or overall survival as compared to external beam alone in the definitive treatment of inoperable lung cancer. In the palliative setting, brachytherapy can provide prompt relief of obstructive symptoms and hemoptysis in the majority of patients.
J. Surg. Oncol. 1998;67:60–70.

KEY WORDS: lung cancer; brachytherapy; radiation therapy

INTRODUCTION

The majority of patients with lung cancer present with locally advanced or metastatic disease not amenable to curative surgical resection. Other patients undergo attempted resection with questionable or involved margins and a high risk of subsequent local recurrence. Despite the increased survival and local control recently observed with combined chemotherapy and external beam radiation for locally advanced inoperable lung cancer, there remains considerable room for improvement [1]. Conventional external beam radiation to 65 Gy with chemotherapy is still associated with a low rate of complete histologic response, in the range of 20% [2]. Many patients die with uncontrolled intrathoracic disease. The high rate of local tumor recurrence or persistence with definitive external beam radiation has led to dose-intensification studies. Conversely, when the goal is palliation, treatment must be quick, effective, and have a low risk of complications. Brachytherapy has been utilized as a ''boost'' to conventional definitive therapy, as well as an expeditious alternative to other palliative modalities. This review will describe the technical aspects of lung brachytherapy and then summarize the available literature regarding the role of brachytherapy in the definitive or palliative treatment of lung cancer.

BRACHYTHERAPY RATIONALE AND TREATMENT TECHNIQUES

Brachytherapy, the direct application of radioactive sources to the tumor bed, can be performed by implantation of the radioactive source into a mass (interstitial brachytherapy) or by introduction of the source into the lumen (intraluminal or endobronchial brachytherapy). As compared to conventional external beam radiation, brachytherapy offers the potential advantage of providing a higher dose of radiation to the tumor-bearing area relative to the dose to the surrounding normal structures. The ''inverse square law,'' one of the physical characteristics of radioactive isotopes, states that the dose-rate measured at a distance from a point source declines as a function of the inverse square of the distance from the source. For example, the dose-rate 2 cm from a radioactive point source would be one fourth of that measured at 1 cm; the dose-rate at 3 cm only one ninth, etc. A typical arrangement of radioactive sources for lung brachytherapy is a series of small point sources 0.5–1.0 cm

*Correspondence to: Laurie E. Gaspar, MD, Gershenson Radiation Oncology Center, Harper Hospital, 3990 John R, Detroit, MI 48201. Telephone No.: 313-745-9654; Fax No.: 313-745-2314.
Accepted 2 October 1997

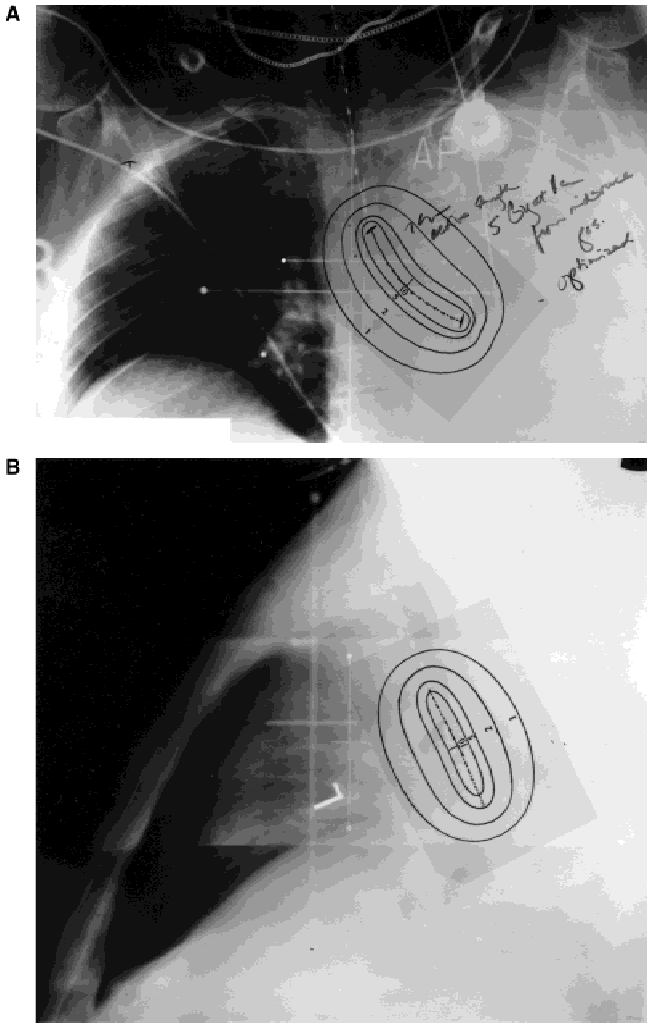

Fig. 1. Anterior-posterior **(A)** and lateral **(B)** simulation film with HDR afterloading catheter and dummy seeds. Isodose lines (10,5,2,1 Gy/hr) overlayed on films. Treatment prescribed to a 7 cm length with the dose (5 Gy) specified 1 cm from the mid-dwell position of the moving source.

apart, forming a line source. The fall-off in dose from a line source is less abrupt than from a single point but, as compared to external beam radiation, brachytherapy delivers a high dose to the primary lung cancer relative to the adjacent normal lung and spinal cord (Fig. 1A,B). The spinal cord typically receives less than 10% of the dose prescribed at 1 cm [3]. The unavoidable consequence of brachytherapy and the inverse square law is the high dose delivered to normal structures adjacent to the tumor, such as normal bronchial mucosa, blood vessels, etc. Depending on tumor location, the mucosa and underlying structures such as the pulmonary vessels may be only 1–2 mm from the brachytherapy source, thereby receiving doses many times the dose prescribed at 1 cm.

Endobronchial or interstitial brachytherapy for lung cancer can be categorized as temporary or permanent. Temporary implants are placed with the intention of removing them at a predetermined interval which may be minutes, hours, or days. Temporary implants can deliver either low, intermediate, or high dose rate radiation which is defined as follows: low dose rate (LDR) less than 2 Gy per hour intermediate dose rate (IDR) 1–12 Gy per hour, high dose rate (HDR) greater than 2 Gy per minute. LDR brachytherapy takes 1–4 days and is usually done on an inpatient basis in one or two sessions. A typical LDR system utilizes an iridium wire or iridium-192 seeds embedded in a Vicryl strand to deliver 0.4–1.0 Gy per hour or approximately 10 Gy per day. IDR brachytherapy, often utilizing cesium-137 pellets, is completed within several hours and is frequently given in several fractions of 5–10 Gy separated by 1–2 weeks. HDR brachytherapy treatment is completed within minutes, and like IDR is frequently given in two to three fractions of 5–10 Gy, requiring repeated bronchoscopies.

An implant is referred to as ''permanent'' if the irradiation is delivered over an infinite period of time. This technique is most appropriate for very LDR interstitial treatment, i.e., the placement of a radioactive source into the tumor or target region where no lumen exists.

Interstitial Brachytherapy Techniques

Several investigators have described the technical aspects of permanent interstitial brachytherapy, the placement of the radioactive source into the tumor or target region where no lumen exists [4–8]. This can be accomplished intraoperatively, transbronchially, or percutaneously. To adhere to radiation safety guidelines, sources such as iodine-125, palladium-103, and gold-193 are used which have low energy gamma rays, small physical size, and short half-lives measured in terms of days. In experienced hands, brachytherapy should add only 30–45 minutes to an operative procedure. Mick applicators are commercially available to insert the seeds manually one-by-one into the target region. However, the risk of subsequent seed movement has led many experienced brachytherapists to recommend that the seeds be in the form of a strand with a Vicryl carrier which can be woven into dexon mesh and secured to the tumor bed [6]. Nori et al. [6] have described the intraoperative technique of sandwiching iodine seeds between sheets of Gelfoam and then securing these in place with dexon/Vicryl mesh. In their experience, the seeds have remained in site despite the fact that the mesh and Gelfoam are absorbed within the surrounding tissues within 6–8 weeks time. Typical permanent implants have an initial dose rate of 0.05–0.1 Gy per hour, delivering total doses in the range of 100–160 Gy at a depth of 0.5–1.0 cm. A size restriction of 6 × 6 cm has been suggested for this permanent implant technique [4]. Transbronchial interstitial permanent implants with gold-198 sources have also been described but utilized only in small numbers of patients [9].

Interstitial HDR brachytherapy can be accomplished

by implanting applicator catheters into the tumor bed. The catheters can be secured to the treatment region with instruments such as the laparoscopic hernia repair stapler. Typically, the HDR brachytherapy is delayed 3–5 days following surgery. Relative to a permanent implant, HDR brachytherapy has the advantage of allowing pathology results to be known prior to irradiation and leisurely computer-assisted treatment planning, with minimal radiation exposure to operating room personnel. Mediastinal HDR brachytherapy has been advocated in the presence of close or positive margins with the dose per fraction at 1 cm in the range of 4–5 Gy. Fractions are generally repeated three to four times during a 2-day period, with an interval of 4–6 hours between treatments [4].

Endobronchial Brachytherapy Techniques

The most common lung brachytherapy technique is endobronchial treatment, delivered from within the lumen by placement of one or two afterloading applicators within the trachea or bronchus. The applicators, sometimes referred to as catheters, typically have a 5 or 6 French external diameter. First a guidewire, passed directly through the operating channel of a fiber optic bronchoscope, must be threaded through the involved airway. Manipulation of the guidewire through a partially obstructed lumen requires skill, particularly within the upper lobe bronchi. Care must be taken to slowly advance the applicator over the guidewire, preferably under direct visual or fluoroscopic control. Temporary pleuritic pain is induced in many patients when the applicator inadvertently touches the pleura; pneuomthorax can result from overvigorous placement. Nd-YAG laser treatment frequently precedes brachytherapy if there is near-complete or complete obstruction to allow passage of the guidewire and applicator. Opinions vary as to whether it is necessary to wait 2–3 days after laser treatment before proceeding with brachytherapy or whether it can be done immediately [10,11].

After placement of the brachytherapy catheter, the bronchoscope is removed and ''dummy'' seeds (an inactive strand of radio-opaque marker pellets) are inserted within the applicator. An orthogonal set of chest X-rays (anterior-posterior and cross-table lateral) are obtained. The target is identified on the films using the visual information obtained that day by the bronchoscopist combined with previous radiological or bronchoscopic findings. The distal extent of the tumor cannot always be visualized by the bronchoscopist and must often be estimated from previous computerized tomography scans, chest X-rays, etc. Brachytherapy is delivered to the endobronchial tumor length with a 1–2 cm proximal and distal margin, i.e., a 4 cm tumor would be treated with a brachytherapy active length of 6–8 cm. The active length refers to the distance between the most proximal and distal radioactive source, or as in the case of HDR brachytherapy, it is the distance between the first and last dwelling point of the stepping iridium source. Treatment is prescribed by the radiation oncologist, usually specified at a depth taken 1 cm from the middle of the active length of the brachytherapy source [12] (Fig. 1). The dummy seeds are then removed from the catheter and replaced manually with either an LDR source or an IDR or HDR inner applicator. HDR remote afterloading machines contain a microprocessor which controls the transfer of the source down the flexible inner applicator to the specified region, and withdraws it automatically into the machine when treatment is complete. Treatment is delivered in a shielded room where the patient and the patient's vital signs and oxygen saturation can be monitored from outside the room with the use of video equipment. Remote afterloading treatment can be interrupted at any time necessary.

Lung brachytherapy has been practiced for many years, but interest in this modality has increased recently due to the availability of small, high-activity sources in computerized, remote afterloading machines, i.e., the radioactive source is placed within the patient while the operators are outside the room. Temporary HDR endobronchial brachytherapy is most widely practiced due to the short time during which an intraluminal catheter is required, as well as the easy operator use and minimal radiation exposure to involved medical personnel. By varying the source position and dwell time, individualized computer-assisted dose distributions conforming to the size and shape of the primary lesion can be generated. This is referred to as dose ''optimization.'' If the target volume is irregularly shaped, such as with a tumor involving a main bronchus extending to involve both the upper and lower lobe orifices, multiple catheters are inserted into the involved lobar bronchi. With the aid of optimization, a homogeneous dose can be delivered at a specified distance from the sources.

CLINICAL RESULTS: DEFINITIVE TREATMENT

Interstitial Brachytherapy

One of the largest experience with interstitial brachytherapy is from Memorial Sloan Kettering Cancer Center (MSKCC), reported by Ginsberg et al. [5]. Between 1974 and 1991, 102 patients with superior sulcus tumors underwent preoperative external beam radiation to a dose of 40 Gy, followed 4 weeks later by thoracotomy with attempted en bloc resection or lobectomy and mediastinal lymph node dissection. Intraoperative interstitial brachytherapy was done only in the presence of close or positive resection margins. Brachytherapy techniques varied over the years, utilizing either a permanent iodine-125 implant to deliver 160 Gy over infinity, or an LDR temporary iridium-192 implant to deliver 30–40 Gy over 3–5 days.

Chemotherapy was also not standardized throughout the years, but was routine in the last few years of study in patients with involved mediastinal lymph nodes. The 5-year survival rate for those patients with negative but close margins was 41%. Brachytherapy did not appear to influence locoregional recurrence or survival in patients with close margins, as compared to a similar group of patients at MSKCC who did not undergo brachytherapy. Of the 55 patients implanted following an incomplete resection, the 5-year survival was only 9%. Local recurrence exceeded 66%, even in those patients in whom a complete resection was obtained prior to brachytherapy. There were no 5-year survivors when tumor involved the great vessels. Other adverse prognostic factors identified included Horner's syndrome, mediastinal nodal involvement, and vertebral body involvement. The authors concluded that surgery should not be attempted if mediastinal nodal disease or incomplete resection is anticipated since survival results with external beam radiation and chemotherapy are comparable. However, in patients undergoing attempted resection, brachytherapy is still recommended at MSKCC if there are close or positive resection margins. Clear support for this approach will await further reports.

HDR interstitial brachytherapy has been utilized to treat peripherally situated primary or metastatic cancers, although the clinical experience is limited to small groups of patients [13]. Brach and colleagues used computed tomography-guided fine needle percutaneous implantation for direct intralesional HDR brachytherapy for small (<2 cm) pulmonary lesions in 20 patients with primary lung cancer or metastatic cancer which involved the lung or chest wall. Due to the small tumor size, frequently only one needle was needed. When more than one needle was required, they were spaced 2 cm apart. The 20–21 gauge needles allowed treatment to be delivered with HDR afterloading machines which contain a particularly small (0.57 external diameter) iridium-192 source. After placement of the afterloading catheters within the needles, the patient was transported to the radiation oncology department where computer-assisted treatment planning was performed. A single dose of 10–20 Gy to the periphery of the tumor was given unless the tumor was adjacent to the pericardium, esophagus, or spinal cord, in which case the total dose was given in two to three fractions over several days. Brachytherapy was usually followed within 2–3 weeks by external beam radiation. If external beam radiation preceded brachytherapy, brachytherapy was delayed 6–8 weeks to allow for maximum tumor regression. The only significant complication reported was pneumothorax, occurring in 6 of the 20 patients implanted. Pneumothorax did not prevent completion of any treatment. The small number of patients treated for different indications with varying treatment schedules does not allow assessment of this innovative brachytherapy technique at this time.

Endobronchial Therapy

Endobronchial brachytherapy has been employed alone as the sole treatment modality or as a boost following conventional external beam radiation. The results of brachytherapy in the treatment of tracheal and major bronchial lesions are usually reported in a combined fashion, making it difficult to make definitive statements about the role of brachytherapy for the less common and difficult to manage entity of cancer of the trachea. Histology does not appear to be an important predictor of tumor response, as brachytherapy for squamous or adenocarcinomas is reported to have similar efficacy [14, 15]. Squamous cell cancers frequently outnumber adenocarcinomas in the intraluminal brachytherapy literature since the majority of centrally located endobronchial tumors are of squamous origin [10,15,16]. Brachytherapy is rarely advocated for small cell cancers due to the low incidence of obstruction from endobronchial mucosal involvement.

Brachytherapy Alone

Brachytherapy alone with curative intent has been evaluated by only a few investigators. Tredaniel et al. [17] reported their experience with HDR endobronchial brachytherapy alone in 29 patients unable to undergo surgery for limited invasive endobronchial tumors. These patients had reasonable pretreatment performance status, were medically fit to undergo numerous flexible bronchoscopies, and had an expected survival of at least 2 months. All tumors were visible within the bronchial lumen, extended no more than 1 cm from the bronchial wall, and were without nodal involvement. Thirteen of these patients had a previous bronchogenic cancer and 16 had relapsed following previous external beam radiation but were still considered potentially curable. The most common brachytherapy dose was 42 Gy at 2 cm, given in 7 Gy fractions, with two fractions one day apart, repeated 15 and 30 days later. No other form of therapy was given. Bronchoscopy 2 months following completion of therapy demonstrated macroscopic complete response in 21 of 25 evaluable patients. Median overall survival had not yet been reached after 23 months of follow-up. Fatal massive hemoptysis occurred in five patients but recurrent disease was suspected in all. No autopsies were performed. Two patients died of massive bronchorrhea, prompting the authors to caution that the dose/fractionation utilized was likely at the upper limits of tolerance of the bronchial mucosa. Although this study suggests that HDR brachytherapy merits further study as the sole treatment for carefully selected patients with minimally invasive tumors, this form of treatment should still be considered unconventional.

TABLE I. HDR Brachytherapy and External Beam Radiation: Definitive Therapy*

Authors	No. of patients	Laser (%)	XRT (Gy)	HDR Gy/fraction[a]	No. of fractions	Fraction interval (wk)	Bronchoscopic response (%)	Median survival (mo)	Complications
Speiser and Spratling [19,20]	50	~24	60	7.5–10	3	2	80	11	7% Hemoptysis 11% Bronchial stenosis
Kohek et al. [10]	39	~52	50–70	5.6	1–5 (usually 2)	1	67	13	5% Hemoptysis 2.5% TE fistula
Zajac et al. [21]	24	0	50–61.2	5–10	3	1	82	12	10% Bronchitis 8% TE fistula
Aygun et al. [15]	62	0	50–61.6	4–6	3–5	1	56	13	15% Hemoptysis
Chang et al. [16]	59	0	60–70	7–8.5	3	2	NA	11	4% Hemoptysis
Cotter et al. [22]	48	0	55–66	2.7–10	2–4	NA	86	12.4	1% Hemoptysis 5% TE fistula

*NA, not available; XRT, external beam radiation; TE, tracheoesophageal.
[a]Dose specified at 1 cm.

Brachytherapy as a Boost

Permanent fibrosis of the normal lung is a frequent late complication of conventional external beam radiation. Limiting the volume of lung tissue irradiated is sometimes difficult, particularly if there is obstruction of a main or lobar bronchus obscuring the tumor margin. Brachytherapy has been utilized prior to external beam radiation to quickly relieve obstruction and reduce the volume of irradiated normal lung. In a retrospective analysis of 15 patients with inoperable stage III nonsmall cell lung carcinoma presenting with malignant airway occlusion, an endobronchial LDR or HDR brachytherapy boost prior to definitive external beam radiation led to a reduction in the normal lung included in the external beam field [18]. Within 10–14 days, brachytherapy resulted in 40% of lungs reaerating completely, and 27% partially. The normal lung subsequently included in the external beam radiation was 25–47% less than would have been included prior to the brachytherapy and reaeration.

Brachytherapy has been used by several investigators as a boost either before, during, or after external beam radiation in the definitive treatment of unresectable nonsmall cell lung cancer. Although HDR, IDR, and LDR regimens have all been described, the experience with HDR brachytherapy boosts is more extensive and is summarized in Table I [10,15,16,19–22]. Patients selected for definitive external beam radiation and a brachytherapy boost were usually medically fit patients with centrally located stage IIIA or IIIB tumors, without weight loss exceeding 10% in the 6 months leading up to diagnosis.

Response to brachytherapy is often assessed by bronchoscopy 1–3 months from completion of treatment. As expected, initial patient performance status, tumor size and stage, and radiation dose are important predictors of outcome [14,15,21]. Aygun observed response rates of 75% in those patients with tumors not visible radiographically as opposed to 36% for those patients with tumors more than 5 cm in diameter [15]. Higher combined doses of brachytherapy and external beam radiation have been associated with an increased endobronchial response and also increased complications [22]. Radiographic response in patients treated to at least 85 Gy vs. lower doses was observed in 70% and 46%, respectively. No complications were seen in patients treated to a dose of 70 Gy, as compared to a 24% complication rate seen in patients receiving more than 85 Gy.

Although the response rates summarized in Table I are good, with partial and complete bronchoscopic response rates in the range of 80%, there are no accepted criteria for defining complete or partial response to brachytherapy. Speiser and Spratling [19] have proposed describing the degree of obstruction of the airway lumen as follows: >50%, 10–50%, and <10% narrowing. The adoption of these grades of obstruction would help in the interpretation of future reports involving lung brachytherapy.

Autopsies have been done in only a small proportion of patients undergoing brachytherapy. This has led to difficulty in differentiating treatment complications from tumor progression. The tabulated complications refer to late serious or fatal events. For tumors in the mainstem or upper lobe bronchus, there appears to be an increased frequency of hemorrhage for right-sided (25%) as opposed to left-sided lesions (25% and 10%), perhaps due to the proximity of the treatment catheter to the pulmonary artery [15].

While dose/fractionation schemes differ in clinical studies, a common regimen in North America would be that utilized by Speiser and Spratling [19]. Until recently, they prescribed 60 Gy external beam radiation given over a 6-week course and three fractions of brachytherapy 7.5 Gy per fraction given weeks 1, 3, and 5 of the external

beam treatment. External beam radiation was omitted on the days of brachytherapy, due to theoretical concerns regarding late toxicity. With this regimen, Speiser and Spratling have reported a median survival of 11 months in patients with locally advanced but potentially curable nonsmall cell cancers of the lung. Radiation-related bronchitis and bronchial stenosis occurred in 11–12%. There was an overall incidence of massive hemoptysis leading to death of 7.3%, which is in the same range as the rate of massive hemoptysis observed following external beam radiation alone for mainstem lesions [23]. Recurrent or residual tumor was suspected or proven post-mortem in all patients dying of massive hemoptysis. This low incidence of treatment-associated complications was observed despite the fact that approximately 30% of patients underwent endobronchial Nd:YAG laser therapy in the 24 hours prior to the first brachytherapy treatment. Although treatment was well tolerated and tumor control within the thorax was maintained in 70% until death, the median survival was only about 12 months which is similar to that expected with external beam radiation alone. Based on these results, Speiser and Spratling concluded that the addition of brachytherapy to external beam radiation has not yet demonstrated an increase in survival. It is difficult to compare their series with that of others because of the high proportion of advanced centrally located tumors in their patient population.

CLINICAL RESULTS: PALLIATION

Brachytherapy is one of several options available for the palliation of endobronchial tumors [24]. Nd:YAG therapy has been advocated as a means of immediate relief of obstruction but depth of coagulation with the Nd:YAG laser is hard to estimate and delayed tumor slough can cause hemorrhage or bronchial obstruction, requiring later mechanical removal of necrotic material through a fiberoptic scope. Other problems include smoke inhalation and the difficulty in applying Nd:YAG to flat or superficial lesions on the bronchial or tracheal wall parallel to the bronchoscope. As a single modality, Nd:YAG laser therapy is associated with rapid tumor regrowth [25,26]. Photodynamic therapy results in solar photosensitivity which may last several months after injection. Relief of obstruction is not immediate and tumor tissue can become edematous, causing further occlusion or slough requiring toilet bronchoscopy 2–4 days after to remove tumor. Depending on the wavelength of light utilized, the penetration is limited to only 0.5–1.0 cm. Endobronchial brachytherapy is a relatively simple and expeditious method of relieving obstruction or maintaining airway patency.

A review of the extensive literature regarding palliative endobronchial brachytherapy is complicated by the variation in the patient population termed ‘‘palliative.’’ Speiser and Spratling [19] consider patients to be palliative if there has been a weight loss of more than 10% in the 6 months prior to diagnosis, if the patient has a poor performance status, has a tumor staged T0, N3, M1 (UICC stage IIIB or IV), or has recurrent disease following definitive external beam radiation. Other authors refer only to patients with stage IV disease or tumors recurrent after full-dose external beam [27]. Tumor stage and/or patient performance factors are difficult to determine from some large reports [28].

Brachytherapy is not always indicated for patients with obstructive symptoms. Early in their experience, Speiser and Spratling [19] found that those patients with obstruction due to extrinsic compression had a poor subjective response to brachytherapy, prompting them to discourage brachytherapy in this subset of patients. They also noted little palliative benefit in patients in poor general condition, i.e., those who are bedridden or with a life expectancy of less than 3 months. A similar observation was made by Zajac et al. [21]; patients spending at least one half the day confined to bed seldom experienced palliation except with regard to hemoptysis.

For simplification, palliative brachytherapy can be evaluated in three settings: 1) brachytherapy alone in newly diagnosed patients, i.e., no previous or additional external beam radiation, 2) brachytherapy in newly diagnosed patients in addition to external beam radiation, or 3) brachytherapy alone in patients who have failed following full-dose external beam radiation.

Palliative Brachytherapy Alone: Newly Diagnosed Patients

One of the largest reported series of patients treated with palliative brachytherapy alone is from the Christie Hospital in Manchester, England [28]. Three hundred and twenty-two patients with inoperable nonsmall cell lung cancers were treated with a single fraction of 15–20 Gy HDR intraluminal brachytherapy, with the dose prescribed 1 cm from the central axis of the catheter. A much smaller group of 17 patients received brachytherapy and concurrent external beam radiation. Patients were deemed inoperable either due to their poor general condition, advanced age or pulmonary function, or the advanced stage of the primary tumor, although the majority of patients had only UICC stage II or III disease. The most common early side effect following treatment was a mild transient exacerbation of cough which usually resolved within 2–3 weeks. Six weeks from completion of treatment, improvement was documented in the following percentage of symptomatic patients: stridor 92%, hemoptysis 88%, cough 62%, dyspnea 60%, pain 50%, pulmonary collapse 46%. Approximately one half of the patients developed subsequent locally recurrent/progressive disease, with or without simultaneous distant metastases. At various times following brachytherapy, 83 bronchoscopies were done in 55 patients. In bronchos-

copies performed within the first 3 months, a complete response to treatment was seen in 80%. Overall, 55% of bronchoscopies identified some degree of mucosal radiation reaction. Fibrosis was commonly identified on bronchoscopies performed more than 6 months following brachytherapy. A dose-response relationship was noted with radiation bronchitis and fibrosis more frequently seen in patients treated to 20 Gy as opposed to 15 Gy. Radiation bronchitis requiring intervention occurred in only two patients. Massive hemoptysis leading to death occurred in 32 patients (8%). Cox multivariate analysis revealed that treatment-related factors associated with subsequent massive hemoptysis were brachytherapy dose more than 15 Gy, prior laser therapy, second brachytherapy treatment, and concurrent external beam irradiation. Twenty of 25 assessable deaths related to hemoptysis had suspected recurrence or residual tumor, but 5 did not. Massive hemoptysis leading to death tended to occur between 9 and 12 months, as opposed to deaths from other causes which usually occurred earlier at 3–6 months. Median survival in the total group of patients was only 6 months, despite the fact that less than 10% of the patients had distant metastases at presentation.

In a small group of 19 patients treated with 15 Gy HDR, Goldman et al. [29] performed a detailed assessment before and after brachytherapy which included chest X-rays, computed tomography of the thorax, bronchoscopy including an obstruction index, 5-minute walking tests, isotope ventilation and perfusion lung scanning, and full lung function tests with maximum inspiratory and expiratory flow-volume loops. Symptomatic relief was reported by 17 of the 19 patients. A collapsed lobe or lung, seen in 13 patients, re-expanded in 9 and bronchoscopy demonstrated increased luminal patency in 18 patients. Isotope lung scans showed significant increases in the percentage of total lung ventilation and perfusion measured over the abnormal lung. This study demonstrated the high correlation between objective and subjective improvement as well as confirmed the palliative benefit of brachytherapy which has been described in much larger groups of patients.

The Manchester experience with brachytherapy suggests that 15 Gy in a single fraction is approaching the upper limits of tolerance of the bronchial mucosa. Most North American centers deliver fractionated HDR brachytherapy, although there is no evidence that this is a more effective or tolerable treatment. There is currently no single accepted dose/fractionation scheme utilized. A German study compared two fractionated HDR regimens; four fractions of 3.8 Gy on a weekly basis and two treatments of 7.2 Gy at a 3-week interval [14]. The majority of patients had not received previous external beam radiation. No significant difference in local control or survival time was found between the two treatment regimens. The incidence of massive hemorrhage was similar between the two dose/fractionation schemes, approximately 21–22%. Hemorrhage or local recurrence led to death in approximately 40–50% of patients in either group. The authors concluded that the shorter treatment schedule was more convenient for patients, did not result in more side effects, and provided equivalent local tumor control.

Speiser and Spratling [19,30] have treated over 100 patients with IDR or HDR brachytherapy alone with palliative intent. Treatment consisted of three or four weekly fractions, 5 or 7.5 Gy per fraction. As might be expected, the median survival was only 5.6 months. Objective response, evaluated bronchoscopically, occurred in 84%. The majority of patients had experienced symptomatic relief by the third fraction of brachytherapy. The frequency of symptomatic relief was as follows: dyspnea 54%, cough 51%, pneumonia 86%, and hemoptysis 94%. Massive hemoptysis was seen in 5.5%. In the palliative setting, Speiser currently recommends three fractions of 7.5 Gy.

Palliative Brachytherapy Boost With External Beam: Newly Diagnosed Patients

Although brachytherapy alone may provide effective palliation for obstructive symptoms secondary to lung cancer, the conventional North American approach for patients with newly diagnosed inoperable lung cancer is still external beam radiation, with or without chemotherapy [31,32]. Based on prospective and retrospective studies, brachytherapy has been advocated by some as a boost to external beam radiation when there is a perceived need to provide rapid relief of major airway obstruction, hemoptysis, or cough due to endobronchial disease [12,19,21]. However, it can be argued that brachytherapy as a boost to external beam radiation is no more effective or expedient in providing palliation than either brachytherapy or external beam alone. Speiser and Spratling [19,30] retrospectively compared the objective and subjective response rates in their palliative HDR brachytherapy patients who had brachytherapy alone (three weekly fractions of 5–7.5 Gy) or the combined therapy of 37.5 Gy in 15 fractions concurrent with brachytherapy. The following subjective improvement was noted: dyspnea 48%, cough 57%, pneumonia 82%, and hemoptysis 97%. No significant difference in objective or subjective response was noted with the addition of laser and/or external radiation to brachytherapy. Similarly, Zajac et al. [21] noted that 30 Gy external beam radiation, given in 2.5–3 Gy fractions, resulted in little objective response compared to that seen during the subsequent HDR brachytherapy of three weekly fractions of 10 Gy. The response observed by the last session of the three weekly fractions was predictive of the final response and further objective response was not usually seen at the follow-up bronchoscopy 6 weeks later. Cur-

TABLE II. LDR Brachytherapy: Palliative for Recurrence Following External Beam Therapy*

Authors	No. of patients	Prior laser (%)	Dose Prior XRT	LDR Gy/ fraction	No. of fractions[a]	Objective response (%)	Subjective response (%)	Median survival (mo)	Late complications (%)
Lo et al. [35]	77	43	NA	45–60[b]	1	59	54	5.1	Hemoptysis 3 TE fistula 1
Mehta et al. [3]	23	18	61 Gy	48	1	NA	Overall 78 Hemoptysis 91 Pneumonia 82 Dyspnea 79 Chest pain 73 Cough 68	5.5	TV fistula 6 TE fistula 3
Raju et al. [34]	39	8	NA	7–28 (usually 20)	1–2	89	Dyspnea 82 Hemoptysis 89 Cough 79 Pneumonia 92	5.0	0

*XRT, external beam radiation; TE, tracheoesophageal; TV, tracheovascular; NA, not available.
[a]Dose specified 1 cm from mid-source position unless otherwise specified.
[b]Dose specified at 2 cm.

rently, external beam radiation in addition to brachytherapy is recommended if there is bulky mediastinal lymphadenopathy. Otherwise, brachytherapy alone is a reasonable option for the palliation of obstructive symptoms.

Palliative Brachytherapy: Recurrences Following External Beam Radiation

Brachytherapy is an accepted treatment for recurrent symptomatic endobronchial disease [3,19,26,27,33–35]. Tables II and III summarize selected reports utilizing LDR or HDR brachytherapy at the time of recurrence. Symptom relief was obtained in approximately 75% of patients, lasting for up to 6 or 7 months in many patients. Bedwinek et al. [27] found that symptom relief was more frequent in those patients who had extrabronchial tumor measuring less than 5 cm in maximum diameter, as compared to those with larger tumors. Objective response was documented in 75–80% of the select subset of patients in these reports who had a follow-up bronchoscopy. Speiser and Spratling [19,20] have observed a significant decrease in bronchoscopic response in patients treated with palliative brachytherapy for relapse following external beam radiation as compared to those who had not received previous external beam radiation, i.e., 70% and 84%, respectively.

Of the series summarized in Tables II and III, an acceptable incidence of severe late complications, including hemoptysis, was reported by most. Concern has been raised regarding the high incidence of hemoptysis reported by Bedwinek et al. [27]. In Bedwinek's series, 32% of patients died of massive hemoptysis occurring 2–56 weeks (median 10 weeks) after brachytherapy. The location of the tumor was the most important predictor of pulmonary hemorrhage since hemoptysis occurred only in patients with tumors in the right upper lobe, right mainstem, or left upper lobe bronchus. The authors discussed several hypotheses which could explain the unexpectedly high complication rate: 1) a high dose of up to 120–150 Gy to the pulmonary arteries due to the close relationship between the bronchi and these arteries resulting in a radiation-induced fistula, 2) tumor involving the nearby vessel wall but acting as a ''plug'' which later leads to a hole if brachytherapy causes tumor shrinkage, or 3) a statistical fluke. Since few other studies have reported such a high incidence of hemorrhage following brachytherapy, it is hoped that the results are a statistical fluke. However, hemorrhage should be listed as a complication of brachytherapy.

NORMAL TISSUE COMPLICATIONS: GRADING AND MANAGEMENT

The variation in airway lumen diameter and the variable position of the treatment catheters within the lumen can result in unexpectedly high doses to the surrounding normal bronchial/tracheal mucosa. This is likely the underlying cause of the severe complications such as hemoptysis, bronchitis, and stenosis observed following brachytherapy.

Brachytherapy-related hemoptysis has been graded simply as massive (usually fatal) or nonmassive. The treatment is the same as for hemoptysis from other causes, i.e., bed rest, codeine, fluid replacement, avoidance of anticoagulants, vascular embolization, etc. Radiation bronchitis and stenosis associated with endobronchial brachytherapy have been well documented, likely due to the tendency to perform follow-up bronchoscopies. It is often difficult to differentiate brachytherapy complications from those related to external beam radiation or laser therapy. Speiser and Spratling [20] have noted that late changes can range from mild mucosal inflammatory response with swelling to fibrosis with cir-

TABLE III. HDR Brachytherapy: Palliative for Recurrence Following External Beam Radiation*

Authors	No. of patients	Prior laser (%)	Dose prior XRT (Gy)	HDR Gy/fraction[a]	No. of fractions	Fraction interval (wk)	Subjective response (%)	Objective response	Median survival	Complications (%)
Lo et al. [33]	59	24	NA	7	3	1	72	93% (15)	3 mo	0
Gauwitz et al. [38]	24	—	⩾55	9	2	2	88	NA	32 wk	Bronchitis 4 Hemoptysis 4
Speiser and Spratling [19]	109	24	NA	5–7.5	3–4	1	Hemoptysis 99 Pneumonia 99 Dyspnea 86 Cough 85	70%	6.2 mo	Hemoptysis 7 Bronchitis 12 Bronchial stenosis 11
Bedwinek et al. [27]	38	—	⩾50	6	3	1	Complete 42 Partial 34 Overall 76	Complete 41% Partial 41% Overall 82% (27)	6.5 mo	Hemoptysis 32

*XRT, external beam radiation; NA, not available.
[a]Dose specified at 1 cm.

cumferential stenosis. Histopathological changes consist of mild mucosal inflammatory response and swelling with amorphous fibrinous and/or eosinophilic debris. Severe reactions are characterized by fibrosis. A grading system to enable comparison of complications between various dose-fractionation regimens has been proposed by Speiser and Spratling [20] (Table IV). The management of brachytherapy-induced bronchitis or stenosis varies with the severity of the reaction. Treatment suggestions according to grade are summarized in Table V.

TABLE IV. Grading of Radiation Bronchitis and Stenosis

Grade 1	Mild mucosal inflammatory response with swelling, characterized by a thin, whitish, circumferential membrane. No significant luminal obstruction. No intervention necessary.
Grade 2	White fibrinous membrane with exudation causing symptoms such as cough and/or obstructive problems requiring therapeutic intervention.
Grade 3	Severe inflammatory response with marked membranous exudate. Multiple debridement or other interventions required to reestablish full lumen of airway.
Grade 4	Greater degree of fibrosis with resulting circumferential stenosis leading to a decrease in lumenal diameter.

TABLE V. Treatment of Radiation Bronchitis

Grade I	Observation
Grade II	Steroids- oral and/or aerosol Fluconazole Saline-diluted bronchodilators Narcotic cough suppressants
Grade III-IV	Balloon or bougie dilatation Laser photoresection Debridement Stents

DISCUSSION

Although lung brachytherapy has been advocated by radiation oncologists for years, recent technological developments in the area of brachytherapy, such as the design of small high-activity iridium-192 sources in remote afterloading machines, have prompted renewed interest in lung brachytherapy. The role of lung brachytherapy is not yet clear since standard or uniform patient/tumor selection criteria do not exist. Few well-conducted randomized studies of lung brachytherapy have been completed. Clinical trials of brachytherapy vs. alternative local modalities such as conformal external beam radiation, bronchial stents, Nd:YAG laser resection, and photodynamic therapy are even less common. The decision to use one local treatment modality over another must take into consideration not only possible survival benefits, but also primary tumor control, rapidity and duration of symptom relief, treatment costs, and acute or chronic toxicity assessment.

Interstitial lung brachytherapy is not used frequently in clinical practice. This may be due to the difficulty in gaining expertise with interstitial techniques, as compared to external beam treatment planning or even endobronchial brachytherapy. The introduction of I-125 with its 60-day half-life and low energy photons have made interstitial brachytherapy more practical. However, at this time there is no proven role for interstitial brachytherapy alone or in combination with other treatment techniques such as surgery, chemotherapy, or external beam.

Endobronchial brachytherapy is widely practiced in the United States, with the lung being one of the most common sites treated with this modality [36]. At the present time, there is no evidence that one dose rate is superior to another in terms of improved local control or decreased morbidity [3,33]. The American Brachy-

therapy Society (ABS) HDR consensus guidelines currently state that although endobronchial brachytherapy has demonstrated efficacy for symptomatic relief of bronchial obstruction and hemoptysis either alone or in combination with external beam radiation, the benefit of brachytherapy in addition to conventional external beam radiation and chemotherapy has yet to be proven [12]. The ABS recommends that brachytherapy for the definitive treatment of lung cancer be done within the context of controlled clinical trials. Outside of clinical trials, the ABS suggests that brachytherapy be reserved for palliation. Although the guidelines do not clearly state the indications for additional external beam radiation in newly diagnosed patients, brachytherapy alone is recommended for recurrences after full-dose external beam. No single dose/fractionation regimen was recommended, noting that regimens vary from 15 Gy in a single fraction to 4 Gy in five fractions. Dose specification 1 cm from the source center was recommended. Nd:YAG laser should precede brachytherapy when there is critical airway narrowing requiring immediate relief. Brachytherapy may be done as early as 24–48 hours following laser therapy [26,37]. Even in the palliative setting, additional brachytherapy is not recommended if there is large vessel involvement by a tumor.

Although endobronchial brachytherapy is frequently utilized to palliate hemoptysis, it is ironic that one of the major concerns regarding lung brachytherapy has been the association between the treatment and subsequent fatal massive hemoptysis observed by several authors [27,28,38]. An unexpectedly high incidence of hemoptysis has not been reported in the majority of clinical studies involving endobronchial brachytherapy. In a retrospective review of 877 autopsy cases of lung cancer treated by means other than brachytherapy, massive hemoptysis leading to death was found to be significantly associated with cavitated squamous cell carcinoma arising in either the right or left main bronchi [23]. Hemoptysis usually preceded external beam radiation therapy and did not appear to be causally related, occurring in approximately 15% of cases of all tumor histologies. Further support for the hypothesis that hemoptysis is related more to tumor involvement of mucosa and vessels is found in the photo laser literature. Macha et al. [39] noted a higher rate of terminal hemorrhage (34.5%) in a group of patients treated with laser resection and external beam radiation, as compared to a matched control group of patients treated with external beam alone (8%). The major difference between the two groups of patients was the endobronchial obstruction from mucosal tumor involvement in the laser group as opposed to extrinsic obstruction in the nonlaser group. Macha et al. concluded that the higher percentage of massive hemorrhage in patients receiving endobronchial laser resection was not directly related to the treatment, but reflected the different patterns of tumor growth with respect to mucosal destruction. The relationship between brachytherapy and subsequent massive hemoptysis can only be clarified if similar case matched control or autopsy studies are conducted on patients who have undergone brachytherapy.

A study by the Radiation Therapy Oncology Group (RTOG) evaluated the palliation provided by external beam radiation to patients with newly diagnosed nonmetastatic nonsmall cell lung cancers [32]. This study by Simpson et al. demonstrated that a short course of external beam radiation such as 30 Gy in 2 weeks provided relief of hemoptysis in 74% of patients, cough in 55%, and dyspnea in 43%. Median survival was in the range of 6 months. As compared to this RTOG study, brachytherapy alone appears to provide equivalent palliation as external beam radiation with a similar survival outcome. Brachytherapy may give more prompt symptomatic relief of obstructive symptoms. Prospective randomized studies of brachytherapy and external beam radiation are clearly needed to directly compare treatment efficacy and toxicity as well as cost-benefit analysis and quality of life issues.

REFERENCES

1. Dillman RO, Seagren SL, Propert KJ, et al.: A randomized trial of induction chemotherapy plus high-dose radiation versus radiation alone in stage III non-small-cell lung cancer. N Engl J Med 1990; 323:940–945.
2. Arriagada R, Le Chevalier T, Quoix E, et al.: ASTRO Plenary: Effect of chemotherapy on locally advanced non-small cell lung carcinoma: A randomized study of 353 patients. Int J Radiat Oncol Biol Phys 1991;20:1183–1190.
3. Mehta M, Petereit D, Chosy L, et al.: Sequential comparison of low dose rate and hyperfractionated high dose rate endobronchial radiation for malignant airway occlusion. Int J Radiat Oncol Biol Phys 1992;23:133–139.
4. Aye RW, Mate TP, Anderson HN, et al.: Extending the limits of lung cancer resection. Am J Surg 1993;165:572–576.
5. Ginsberg RJ, Martini N, Zaman N, et al.: Influence of surgical resection and brachytherapy in the management of superior sulcus tumor. Ann Thorac Surg 1994;57:1440–1445.
6. Nori D, Bains M, Hilaris BS, et al.: New intraoperative brachytherapy techniques for positive or close surgical margins. J Surg Oncol 1989;42:54–59.
7. Hilaris BS, Nori D, Beattie EJ, et al.: Value of perioperative brachytherapy in the management of non-oat cell carcinoma of the lung. Int J Radiat Oncol Biol Phys 1983;9:1161–1166.
8. Mittal BB, Nemcek AA Jr, Sider L: Malignant tumors invading chest wall: Treatment with CT-directed implantation of radioactive seeds. Radiology 1993;186:901–903.
9. Rabie T, Wilson RK, Easley JD, et al.: Palliation of bronchogenic carcinoma with 198 Au implantation using the fiberoptic bronchoscope. Chest 1986;90:641–645.
10. Kohek PH, Pakisch B, Glanzer H: Intraluminal irradiation in the treatment of malignant airway obstruction. Eur J Surg Oncol 1994;20:674–680.
11. Speiser BA, Spratling L: Intermediate dose rate remote afterloading brachytherapy for intraluminal control of bronchogenic carcinoma. Int J Radiat Oncol Biol Phys 1990;18:1443–1448.
12. Nag S, Abitbol AA, Anderson LL, et al.: Consensus guidelines for high dose rate remote brachytherapy in cervical, endometrial, and endobronchial tumors. Int J Radiat Oncol Biol Phys 1993;27: 1241–1244.
13. Brach B, Buhler C, Hayman MH, et al.: Percutaneous computed

tomography-guided fine needle brachytherapy of pulmonary malignancies. Chest 1994;106:268–274.
14. Huber RM, Fischer R, Hautmann H, et al.: Palliative endobronchial brachytherapy for central lung tumors. A prospective, randomized comparison of two fractionation schedules. Chest 1995; 107:463–470.
15. Aygun C, Weiner S, Scariato A, et al.: Treatment of non-small cell lung cancer with external beam radiotherapy and high dose rate brachytherapy. Int J Radiat Oncol Biol Phys 1992;23:127–132.
16. Chang LL, Horvath J, Peyton W, et al.: High dose rate afterloading intraluminal brachytherapy in malignant airway obstruction of lung cancer. Int J Radiat Oncol Biol Phys 1994;28:589–596.
17. Tredaniel J, Hennequin C, Zalcman G, et al.: Prolonged survival after high-dose rate endobronchial radiation for malignant airway obstruction. Chest 1994;105:767–772.
18. Bastin KT, Mehta MP, Kinsella TJ: Thoracic volume radiation sparing following endobronchial brachytherapy: A quantitative analysis. Int J Radiat Oncol Biol Phys 1993;25:703–707.
19. Speiser BL, Spratling L: Remote afterloading brachytherapy for the local control of endobronchial carcinoma. Int J Radiat Oncol Biol Phys 1993;25:579–587.
20. Speiser BL, Spratling L: Radiation bronchitis and stenosis secondary to high dose rate endobronchial irradiation. Int J Radiat Oncol Biol Phys 1993;25:589–597.
21. Zajac AJ, Kahn ML, Heiser D, et al.: High-dose-rate intraluminal brachytherapy in the treatment of endobronchial malignancy. Work in progress. Radiology 1993;187:571–575.
22. Cotter GW, Lariscy C, Ellingwood KE, et al.: Inoperable endobronchial obstructing lung cancer treated with combined endobronchial and external beam irradiation: A dosimetric analysis. Int J Radiat Oncol Biol Phys 1993;27:531–535.
23. Miller RR, McGregor DH: Hemorrhage from carcinoma of the lung. Cancer 1980;46:200–205.
24. McCaughan JS Jr, Hawley PC, Walker J: Management of endobronchial tumors: A comparative study. Semin Surg Oncol 1989; 5:38–47.
25. Shea JM, Allen RP, Tharratt RS, et al.: Survival of patients undergoing Nd:YAG laser therapy compared with Nd:YAG laser therapy and brachytherapy for malignant airway disease. Chest 1993;103:1028–1031.
26. Miller JI, Phillips TW: Neodymium:YAG laser and brachytherapy in the management of inoperative bronchogenic carcinoma. Ann Thorac Surg 1990;50:190–196.
27. Bedwinek J, Petty A, Bruton C: The sue of high dose rate endobronchial brachytherapy to palliate symptomatic endobronchial recurrence of previously irradiated bronchogenic carcinoma. Int J Radiat Oncol Biol Phys 1991;22:23–30.
28. Gollins SW, Ryder WDJ, Burt PA, et al.: Massive hemoptysis death and other morbidity associated with high dose rate intraluminal radiotherapy for carcinoma of the bronchus. Radiother Oncol 1996;39:105–116.
29. Goldman JM, Bulman AS, Rathmell AJ, et al.: Physiological effect of endobronchial radiotherapy in patients with major airway occlusion by carcinoma. Thorax 1993;48:110–114.
30. Speiser BL: Brachytherapy in Bronchogenic Carcinoma. Proceedings of the American Brachytherapy Society, School of Brachytherapy. Arizona, Phoenix, December 1995.
31. Sause WT, Scott C, Taylor S, et al.: RTOG-88-08 and ECOG 4588: Preliminary results of a phase III trial in regionally advanced, unresectable non-small-cell lung cancer. J Natl Cancer Inst 1995;87:198–205.
32. Simpson JR, Francis ME, Perez-Tamayo R, et al.: Palliative radiotherapy for inoperable carcinoma of the lung: Final report of a RTOG multi-institutional trial. Int J Radiat Oncol Biol Phys 1985; 11:751–758.
33. Lo TCM, Girshovich L, Healey GA, et al.: Lose dose rate versus high dose rate intraluminal brachytherapy for malignant endobronchial tumors. Radiother Oncol 1995;35:103–197.
34. Raju PI, Roy T, McDonald RD, et al.: Ir-192, low dose rate endobronchial brachytherapy in the treatment of malignant airway obstruction. Int J Radiat Oncol Biol Phys 1993;27:677–680.
35. Lo TCM, Beamis JF, Weinstein RS, et al.: Intraluminal low-dose rate brachytherapy for malignant endobronchial obstruction. Radiother Oncol 1992;23:16–20.
36. Nag S, Owen JB, Farnan N, et al.: Survey of brachytherapy practice in the United States: A report of the Clinical Research Committee of the American Endocurietherapy Society. Int J Radiat Oncol Biol Phys 1995;31:103–107.
37. Khanavkar B, Stern P, Alberti W, et al.: Complications associated with brachytherapy alone or with laser in lung cancer. Chest 1991; 99:1062–1065.
38. Gauwitz M, Ellerbroek N, Komaki R, et al.: High dose endobronchial irradiation in recurrent bronchogenic carcinoma. Int J Radiat Oncol Biol Phys 1992;23:397–400.
39. Macha HN, Becker KO, Kemmer HP: Pattern of failure and survival in endobronchial laser resection. A matched pair study. Chest 1994;105:1668–1672.